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PREPARATION AND EVALUATION OF OCULAR INSERTS OF FLURBIPROFEN FOR CONTROLLED DRUG DELIVERY

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ABSTRACT

The Aim and Objective of the present study is to formulate and evaluate the ocular Inserts of flurbiprofen using different polymers Such as HPMC, Eudragit L100 at various concentrations and combinations using dibutylphthalate as plasticizer. Different formulations were prepared and evaluated for thickness, moisture uptake, weight, Drug content, surface pH.IR spectral analysis showed that there is no interaction of Drug with polymer which indicates the intactness of drug in the formulation. Keywords: flurbiprofen, Hydroxypropymethylcellulose, ocular inserts, Eudragit L100, Dibutylphthalate.

INTRODUCTION

Drugs administered in traditional topical ophthalmic formulation such as aqueous eye drops have poor bioavailability due to rapid precorneal elimination. To reach therapeutic levels frequent instillation of the drug are required, leading to a low patient compliance. Furthermore, the drug level in the tear film is pulsed with an initial period of overdosing, followed by a longer period of under dosing. Generally, efforts have been directed along the following lines:

1. Prolongation of the ocular residence time of the medicine.
2. Enhancement of corneal permeability (enhancer approach).
3. Increasing drug penetration characteristic (chemical Approach).
4. Use of Nanoparticle preparation.
5. Use of Liposomes preparation.

The ocular inserts, which are solid devices placed in the cul-de-sac of the eye in comparison with liquid formulation might present valuable advantages, such as:

- Increased ocular permanence with respect to standard vehicles hence prolonged drug activity and a higher drug bioavailability.
- Increased ocular contact time.
- Accurate dosing (theoretically all of the drug is retained at the absorption site);
- Capacity to provide, in some cases, a constant rate of drug release;
- Possible reduction to systemic absorption, which occurs freely with standard eye –drops via the nasal mucosa;
- Better patient compliance, resulting from a reduced frequency of medication and a lower incidence of visual and systemic side effects;
- Possibility of targeting internal ocular tissues through non-corneal conjunctival-scleral penetration routes; and.
- Increased shelf life with respect to eye –drops due to the absence of water. Another potential advantage of ocular insert therapy is the possibility of promoting non-corneal drug penetration, thus increasing the efficacy of some hydrophilic drugs that are poorly absorbed through the cornea.

Flurbiprofen is a group of Non-steroidal anti-inflammatory drugs. It is mainly employed for the inhibition of intraoperative miosis and post-operative inflammation in cataract surgery. In the study an attempt was made to prepare flurbiprofen ocular inserts with the target of increasing the contact time, reducing the frequency of administration, improving patient compliance and obtaining greater therapeutic efficacy.

MATERIALS AND METHODS

Flurbiprofen was procured as gift sample from Combitic Global Caplet Pvt. Ltd. Sonipat (Haryana). Polymers such HPMC and Eudragit L100 were obtained as gift samples from Combitic Global Caplet Pvt. Ltd. Sonipat (Haryana) and Excellent Pharmatech Vikas puri, New Delhi.

Preparation of the Drug Reservoir

The reservoir containing 200mg of Flurbiprofen with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 16ml capacity and 8cm

diameter (an area of 50.24 cm^2), circular films of 9mm (0.9cm) diameter (an area of 0.63 cm^2) each containing 2.006 mg (theoretical) drug were cut. (Table 1)

Preparation of the Rate Controlling Membrane

The rate controlling membrane was casted on Petri dish using different polymers and dibutylphthalate (30%w/w of polymer) as plasticizer and circular membrane of 10mm (1cm) diameter were cut.

Sealing

The drug reservoir was sandwiched in between the two rate controlling membranes and sealing was done by applying chloroform on the edges of the rate controlling membrane so that both the sides of the drug reservoir were sealed to control the release from periphery.

Table 1: Comparison of various polymers in different formulations per ring.

Formulation code	Rate Controlling Membrane		Drug Reservoir	Plasticizer
	HPMC	Eudragit L100	HPMC	Dibutylphthalate
F1	-	3 %	3 %	30% w/w
F2	-	4 %	3 %	30% w/w
F3	-	5 %	3 %	30% w/w
F4	3 %	-	3 %	30% w/w
F5	4 %	-	3 %	30% w/w
F6	5 %	-	3 %	30% w/w

Characterization of prepared ocular inserts

Ocuserts prepared were evaluated for different parameters as follows

1. Thickness

Thickness was measured using a screw gauge at different places of the Ocuserts and the average was calculated.

2. Weight

Weight was calculated on Digital balance. Three Ocuserts were weighed individually and the average weight was calculated.

3. Drug content

Three Ocuserts were taken and cut into small pieces, put into 100ml buffer (pH7.4) and shaken continuously until they dissolve. The solution was ultrasonicated for 15 minutes. After filtration, the drug was suitably diluted and analyzed at 276nm in UV visible spectrophotometer.

4. Folding Endurance

Folding Endurance was determined by repeatedly folding the film at the same place till breaking or appearance of breaking signs. The number of times the film could be folded at the same place without breaking gives the folding endurance value.

5. Moisture Uptake

The Ocuserts were subjected to desiccation over calcium chloride at room temperature for 48h.These Ocuserts were then weighed and the weight was recorded as initial weight. The Ocuserts were then exposed to75% relative humidity (a saturated solution of ammonium chloride) in a desiccator until a constant weight of the Ocuserts was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

6. Surface pH

The Ocuserts were first allowed to swell by keeping them in contact with 5ml of distilled water for one hour in petridish. pH was noted by bringing the glass electrode near the surface of the formulation (Ocuserts) and allowing it to equilibrate for one minute.[9]

7. In-Vitro Drug Release

In vitro release of drug from Ocuserts was studied using an apparatus similar to that of the diffusion cell. The drug preparation was kept in a glass tube having a diameter of 3cms and both sides open. The open end was tied with semipermeable membrane and then preparation was inserted into it. The tube was tied to a stand and fixed to such a level so that the surface of membrane touches the brim of dissolution medium in beaker (receptor compartment). The dissolution medium (50ml) used was phosphate buffer of pH 7.4. The medium in the receptor compartment was agitated using a magnetic stirrer at 50rpm±4% maintaining a temperature at 370C±10. After specified intervals of time; 3 ml of the sample was taken and replaced with fresh dissolution medium. Then after suitable dilution the absorbance of the sample was taken against blank at 276 nm in UV visible spectrophotometer.

RESULTS AND DISCUSSION

In the present study efforts were made is to formulate and evaluate the ocular Inserts of Flurbiprofen using different polymers such as HPMC, Eudragit L100 at various concentrations and combinations using dibutylphthalate as plasticizer by solvent casting technique. The drug delivery system was designed as diffusion and erosion controlled with predominately first order kinetics and release was controlled by using polymeric rate controlling membrane. The physiochemical evaluation (Table2) indicates that the thickness measured for different formulations (F1, F2, F3, F4, F5 and F6) was in the range of 0.44 to 0.55mm.Formultion F1 was thinnest (0.44mm) while F6 was thickest (0.55mm).Formulation F1 was composed of 3% HPMC in Rate controlling membrane and 3% HPMC in Drug Reservoir while F6 contained with 5% Eudragit

L100 in Rate controlling membrane and 3% HPMC in drug reservoir. Weight of ophthalmic inserts was in the range of 50.66 to 78mg. The drug content was found from 1.64mg to 2.19mg as compared to theoretical 2mg of drug to be incorporated in each Ocuserts. The weight and drug content results showed less extent of patch variability. Folding endurance of a film is a measure of breaking strength and endurance. This is the number of times the film may be folded at one place until it breaks or sign of breakage appears. This was in the range of 48.33 to 65 times. The folding endurance results shows enough strength of Ocuserts to withstand handling shocks. Sometimes Ocuserts comprises of hydrophilic polymers and likely to gain moisture from environment. Hence, it becomes imperative to measure moisture uptake extent for such formulation.

Table 2: Comparative evaluation of formulated Ocuserts with different proportions of polymers (Values are mean ±SEM of three experiments in each group).

Formulation code	Thickness (mm)	Weight (mg)	Drug content (mg)	Folding endurance	Moisture uptake	Surface pH
F1	0.44± 0.017	57.66± 1.202	1.89±0.048	48.33±1.667	5.72±0.469	7.02± 0.020
F2	0.51±0.020	60.33± 1.453	2.19±0.024	65±2.887	7.42±0.389	7.17± 0.055
F3	0.53±0.037	76.66± 0.881	1.77±0.010	54.33±1.764	8.69±0.465	7.18± 0.040
F4	0.48 ±0.014	50.66 ± 3.480	1.64 ±0.020	45 ±2.906	4.47±0.396	6.68±0.225
F5	0.52 ±0.027	76 ±0.881	2.04 ±0.147	54.33± 1.764	5.17±0.840	7.18 ± 0.040
F6	0.55 ±0.023	78 ±1.856	1.82 ±0.041	58.33 ± 1.667	6.03±0.438	7.14 ± 0.017

In-Vitro Drug Release studies were carried out for 11 hours for all formulations (figure 3). To know the mechanism of drug release from these formulations, the data were treated according to zero order (cumulative % of the drug released vs. time), First order (log cumulative % of drug remaining vs. time), Highuchi,s model (cumulative % of the drug released vs. Square root of time) and Korsmeyer's model(log cumulative % of drug released vs log time)[10] After 11 hours the cumulative drug release from formulation F1, F2, F3, F4, F5 and F6 was found to be 48.52%, 38.99%, 31.08%, 43.11%, 31.96%, and 27.01%, respectively. Drug release from F 1, F2 and F4 was faster compared to formulation F3, F5 and F6 during 11 hr. The comparative slow release of drug formulation from F3, F5 and F6 may be due to slow diffusion of drug from the combined hinderence of HPMC and Eudragit L-100 used in higher concentration in these formulations. It is evident from the correlation coefficients for zero order model (Table 3) that neither of the above six formulations shows a perfect or complete zero order pattern. The values of R^2 for High chi's model (0.9640 to 0.9922) also suggest the same result .When the data was plotted according to first order equation, the formulations showed a fair linearity, with R^2 values between 0.9468 to 0.9916.In order to confirm the release kinetics of the formulations the data was fit into Korsmeyer's equation. As is evident from Korsmeyer's equation that for all the formulations the value of n (slope value of log mt/m∞) is less than 1(0.47 to 0.85), which further confirms that release rate is not independent of time. In other words, none of formulation obeys zero order equation (case II transport). For formulations F1 to F3, the value of n obtained was between 0.74 to 0.85, which indicates that there is a coupling diffusion and erosion mechanism (anomalous diffusion/non-Fickian transport) in these formulations. Presence of swellable polymer (HPMC) within such formulations might be responsible for the drug release controlled by more than one process. For formulations F3 to F5 the value of n obtained was between 0.47 to 0.63, which implicates that diffusion is the probable mechanism of drug release in these formulations. The presence of plastic polymer Eudragit L100 might be responsible for diffusion type (Fickian diffusion) of drug release mechanism from such formulations. On the basis of above drug release studies, it may be stated that drug release from the formulation (F4, F5, F6) is diffusion controlled and anomalous diffusion controlled (F1, F2, F3) with predominately first order kinetics. On the basis of the drug release study it was seen that maximum amount of drug is release within 24hrs (96.86%) from formulation F1 as compared to rest of the formulations. Further it has got minimum thickness (0.44mm) and other parameters are also within the limit i.e. it will not produce any discomfort upon insertion. So, formulation F1 containing 3% HPMC in Rate controlling membrane and 3% HPMC in Drug Reservoir seems best optimized formulation among the six formulated Formulations.

CONCLUSION

Conventional ocular drug delivery such as eye drops, ointments, gels etc; have got various disadvantages like Precorneal loss, Evaporation by tears, Drug-protein interaction, Drug metabolism, Drainage, Induced lacrimation, Sticking of eye lids, Poor patient compliance, blurred vision; systemic side effects etc; Utilization of the principles of controlled release by means of ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence time. Thus, reducing frequency of administration & hence increasing patient compliance. Besides the systemic side effects of the drug taken (Diclofenac sodium) could be overcome by utilizing the ophthalmic insert approach. Various formulations of flurbiprofen ocular inserts were prepared using solvent casting method and were evaluated for various physicochemical parameters and Drug release. Formulation F1composed of 3% HPMC in Rate controlling membrane and 3%

HPMC in Drug Reservoir has achieved the target of present study such as increase residence time, prolonged drug release, reduction in frequency of administration and thus may improve the patient compliance. So, by formulation of Ocuserts the undesirable side effects of conventional dosage forms like frequent administration, poor availability, massive and unpredictable doses, drainage of medication by tear and nasolacrimal fluid, visual and systemic side effects can be overcomed. Thus, the formulated Ocuserts will eliminate such undesirable effects and will provide the therapeutic effect over a prolonged period of time. Thus, will increase the patient compliance and therapeutic efficacy with minimal or no side effects. Further work may be carried out to establish the therapeutic utility of this system by pharmacokinetic and pharmacodynamic studies in human beings.

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